REMARKS

Claims 1-11 were pending in the present application. Claims 1-7 and 10 have been amended herein, claims 8-9 and 11 have been canceled herein, and new claims 12-23 have been added herein. Support for amended claims 1-7 and 10, and new claims 12-23 can be found throughout the specification and original claims. No new matter has been added. Upon entry of the present amendments, claims 1-7, 10, and 12-23 will be pending.

I. The Claimed Invention is Not Indefinite

Claim 9 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because it is allegedly unclear what method/process Applicants are intending to encompass. *See* Action at page 2. Although Applicants respectfully disagree with the allegation, claim 9 has been canceled herein rendering its rejection moot. Accordingly, Applicants respectfully assert that the claimed invention is clear and request that the claim rejection be withdrawn.

II. The Claimed Invention is Not Obvious

Claims 1-7 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Stevenson et al., 4,4-Disubsituted Piperidine High-Affinity NK_1 Antagonists: Structure-Activity Relationships and in Vivo Activity, *Journal of Medicinal Chemisty*, 1998, 41, 4623-4635 (hereinafter the "Stevenson reference"). The Action alleges that it would be routine for the chemist to replace phenyl with naphthyl because "Stevenson suggests that lipophilicity of the aryl moiety is important since compound **49** bearing the lipophilic CF_3 group has increased potency over compound **48**." *See* Action at page 5. Applicants respectfully disagree.

The Action's characterization of the Stevenson reference is misguided. The Stevenson reference does not suggest, as the Action alleges, that naphthyl being slightly more lipophilic [than phenyl] would have increased potency. The Stevenson reference examined substitution of the benzyl ether side chain, and not substitution of the entire aryl moiety. The Stevenson reference also reports that monosubstituted benzyl ethers with a large lipophilic substituent in the *meta* position suffer a significant loss in binding affinity (*See* Stevenson reference at page 4625). Thus, the Stevenson reference does not support a general rule that increased lipophilicity means increased potency for the compounds described therein. Accordingly, one skilled in the art

would not be motivated to modify the compounds described in the Stevenson reference to obtain the compounds as claimed by Applicants.

In light of the foregoing discussion, Applicants respectfully assert that the claimed invention is not obvious and request that the claim rejection be withdrawn.

III. The Claimed Invention is Enabled

Claims 7, 8, and 10-11 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. In particular, the Action alleges that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully request reconsideration thereof because one skilled in the art would able to make and/or use the invention without undue experimentation.

While conceding that the Ryckmans article (Ryckmans et al., *Bioorg. Med. Chem. Lett.* (2002), 12, 261) suggests that Applicants' compounds might be useful for the treatment of depression, the Action asserts that the Rosenzwieg-Lipson article (Rosensweig-Lipton et al., *Pharmacology & Therapeutics* (2007), 113, 134-153) suggests that "the state of the art in the area of these dual antagonists is murky at best" (Action at page 8). The Action further asserts that "even if these compounds were evaluated simply as NK_1 antagonists" that it would "be unlikely that one of skill in the art would know what to do with these compounds," based on failed trials in the McLean article (McLean, S., *Current Pharmaceutical Design* (2005), 11, 1529) (Action at page 8). Applicants respectfully disagree.

As will be recognized, the enablement requirement of § 112 is satisfied so long as a disclosure contains sufficient information that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (the legal standard for enablement under §112 is whether one skilled in the art would be able to practice the invention without undue experimentation). In this respect, the following statement from *In re Marzocchi*, is noteworthy:

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter

> sought to be patented **must** be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling.
>
> ... it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971) (emphasis added). Thus, any assertion by the Patent Office that an enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974).

The Office has not carried its burden under *In re Marzocchi*. Further, the claimed methods can be used without undue experimentation. As asserted by Applicants' specification, the compounds have both NK_1 antagonist and serotonin reuptake inhibitory (SRI) activity. There is ample evidence of the efficacy of NK_1 antagonists and SRI's for treating depression and anxiety. For example, the McLean article summarizes the results of 19 positive preclinical studies showing the anxiolytic effect of NK_1 antagonists and 14 positive studies showing the antidepressant effect of NK_1 antagonists, all published prior to the filing date of the present application (McLean, Table 2 at pages 1536-37). The anxiolytic and antidepressant effect of NK_1 antagonists is further supported by the articles cited by Applicants' specification, showing the involvement of NK_1 receptors in depression and a decrease in the anxiety behavior of mice following administration of NK_1 antagonists (Papp, et al., *Behav. Brain Res.* 115:19 (2000); and Santarelli, et al., *Proc. Nat. Acad. Sci.* 98:1912 (2001); cited in the specification at page 2, lines 1-4). Moreover, serotonin reuptake inhibitors were well-known to have efficacy in treating anxiety and depression (Boerner and Moeller, *Pharmacopsychiatry*, 32(4):119-26 (1999)). Hence, there is a clear link between the treatment of depression and anxiety and NK_1 antagonist

and serotonin reuptake inhibition activity. Accordingly, one of skill in the art would be able to practice the claimed invention without undue experimentation.

In light of this evidence, the sections of Rosenzwieg-Lipson and McLean cited by the Examiner fail to provide sufficient evidence to doubt the enablement of the claimed invention, as amended. As to McLean, the Office points to a statement in the article that "[t]o date there are three positive trials in depression, one positive trial in panic, several failed trials and at least 2 negative studies" (Action at page 8; McLean at page 1542). However, in the allegedly "failed" trial for MK-869, a dose dependent decrease in depression symptoms in subjects was observed, leading the reviewers to suggest that MK-869 would actually be effective for subjects with greater depression (McLean at page 1541). In the single negative trial for MK-869, McLean indicates that the report was gleaned from the "lay press" and that "details were not available" (McLean at page 1541). Similarly, in the negative trial for L-75927, McLean indicates that the response to paroxetine, which is indicated for depression, also failed to distinguish from placebo (McLean at page 1541). Further, Applicants respectfully assert that clinical trials may fail for a variety of reasons, including safety concerns which are outside the purview of the U.S. Patent and Trademark Office. *Scott v. Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2d 1115, 1120 (Fed. Cir. 1994). Moreover, McLean does not take into account the effect of serotonin reuptake inhibitory activity.

Although Rosenzwieg-Lipson summarizes the failure of one Phase III depression trial for a single NK_1 antagonist (aprepitant) adminstered alone, it also states that "NK-1 antagonists have been shown to potentiate the neurochemical effects of SSRIs in preclinical studies." (Action at pages 7-8; Rosenzwieg-Lipson article, page 140). Hence, Rosenzwieg-Lipson supports Applicants' assertion that the claimed invention is enabled.

In light of the foregoing discussion, Applicants respectfully assert that claimed invention meets the requirements of 35 U.S.C. § 112, first paragraph, and request that the claim rejection be withdrawn.

IV. The Claimed Invention is Supported by Ample Written Description

Claims 1-7 stand rejected under 35 U.S.C § 112, first paragraph, as failing to comply with the written description requirement, because it is alleged that Applicants are attempting to

claim a compound by what it does rather than what it actually is. *See* Action at page 9. Although Applicants respectfully disagree with the allegation, solely to expedite prosecution and without disclaimer of subject matter, claims 1-7 have been amended. Accordingly, Applicants respectfully assert that the claimed invention meets the written description requirement and request that the claim rejection be withdrawn.

V. Non-statutory Double-Patenting

Claims 1-11 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-10 of copending Application No. 10/525,303 in view of the Stevenson reference. The Action alleges that copending Application No. 10/525,303 teaches compounds, compositions, and methods with compounds that are the amide analogs of the compounds of the instant case that have the same utility. The rejection is currently provisional. Applicants respectfully request that the rejection be withdrawn in view of Applicants' comments above in regard to the Stevenson reference.

VI. Conclusion

Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (610) 640-7859 to resolve any remaining issues.

Respectfully submitted,

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